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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,837	09/04/2001	Kenya Shitara	249-188	4386

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EXAMINER	
YAEN, CHRISTOPHER H	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,837	SHITARA ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *1-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/25/01 & 6/16/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Re: Shitara *et al*
Priority Date: 04 March 1999

1. The amendment filed 6/16/2004 is acknowledged and entered into the record. Accordingly, claims 30-32 are newly added.

2. Claims 1-32 pending, claims 1-21 are withdrawn as being drawn to a non-elected invention(s). Applicant is reminded to cancel claims drawn to non-elected subject matter.

3. Claims 22-32 examined on the merits.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

5. The Information Disclosure Statement filed 6/16/2004 is acknowledged and considered. A signed copy of the IDS is attached hereto. In addition, as requested by the applicant, a signed copy of the IDS filed, 10/25/2001 which lists the document EP 0882799A1 is also attached hereto.

Claim Rejections Maintained - 35 USC § 112, 1st paragraph

6. The rejection of claims 22-29 and now newly added claims 30-32 under 35 USC § 112, 1st paragraph is maintained for the reasons of record. Applicant's submission of the declaration filed 6/16/2004 (herein Shitara Declaration) is acknowledged and considered. Applicant argues that in Shitara Declaration, that the antibodies disclosed

in the instant invention are capable of exhibiting ADCC on leukemic cell lines, and that such ADCC is indicative of anti-tumor activity as evidenced by Steplewski *et al.* Applicant's arguments and declaration have been carefully considered but are not deemed persuasive to overcome the rejection of record. Reasonable guidance must be provided in the specification for one of skill in the art to practice the instant invention. However, in the instant case, the specification is devoid of any indication of how one of skill in the art is to set forth in the practice of treating a disease associated with a tumorigenic change of a hematopoietic cell. The specification has only disclosed the production of an flt-1 antibody, the detection and comparison of the flt-1 receptor in various cell lines and the comparison of antibody reactivity. The specification failed to provide sufficient guidance on how the detection or indication of the flt-1 receptor can be correlated to a method of treating a disease associated with a tumorigenic change in a hematopoietic cell. The declaration filed by the applicant does not provide a reasonable nexus between the detection of flt-1 in leukemic cells and the ability of antibodies to undergo a mechanism of ADCC. One of skill in the art would not be able to make the leap of faith from detection to treatment based simply on the fact that in leukemic cells there is a presence of an flt-1 receptor. Although Steplewski *et al* teaches that isoforms of IgG antibodies are capable of eliciting anti-tumor effect on effector cells, this does not definitively indicate the presence of flt-1 on leukemic cells nor the use of an anti-flt-1 antibody for tumor cell destruction. No nexus has been provided in the specification nor in the prior art that teaches such a correlation can be made.

Applicant also traverses points made by the examiner with regard to the unpredictable nature of correlating in vitro experiments to in vivo outcome by arguing that cell-cell contacts are irrelevant to blood neoplasms. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. Contrary to applicant's statements, not all hematopoietic neoplasms are "immersed in blood" (i.e. multiple myeloma – a tumor which is found primarily in the bone marrow) or are free from "cell-cell" interactions. For example, myeloma cells have been known to interact with the microenvironment of the bone marrow often forming cell-cell contacts (see Bellamy *et al* Cancer Res. 1999;59:728-733 - see in particular page 732). However, the point of the references cited in the prior office action was to underscore the unpredictable nature of correlating in vitro result to in vivo applicability because there are many fundamental differences between the in vitro and in vivo environment.

Applicant also argues that the instant invention is enabling based on the rejection under 35 USC 102(e), because any invention which is placed in the art is presumed enabling. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. For the purposes of the instant rejection, the claims are read to the extent that the method is drawn to a method of treating diseases associated with a tumorigenic change to a hematopoietic cell. On the other hand, the art rejection under 35 USC 102(e) is read to the extent that the claims read on the administration of an anti-flt1 antibody to a patient. Because the interpretation of the claims for the 102(e) rejection only requires a single step (i.e.

administration to a patient) and does not specifically limit the type of patient to which the administration is to take place, the art does not enable the instant invention to the extent that is reads on treating a disease associated with a tumorigenic change in a hematopoeitic cell.

Thus the rejection under 35 USC 112, 1st paragraph is maintained for the reasons of record.

Double Patenting Maintained

7. The rejection of claims 22-28 under the judicially created doctrine of provisional obviousness-type double patenting is maintained for the reasons of record. Applicant argues the rejection should be withdrawn because the rejection is "inappropriate", and that at a minimum the rejection should be held in abeyance until allowable subject matter is identified. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. Because the applicant has not specifically argued why the rejection is "inappropriate" the rejection is maintained for the reasons of record. Applicant's request to hold the rejection in abeyance is noted.

Claim Rejections Maintained - 35 USC § 102

8. The rejection of claims 22-24 under 35 USC § 102(e) is maintained for the reasons of record. Applicant argues that the rejection is inconsistent with the rejection under 35 USC 112, 1st paragraph. In addition applicant argues that Shitara *et al* does not relate to treatment of tumorigenic changes in hematopoietic cells, but rather to

methods of treating angiogenesis. Applicant's arguments have been carefully considered but are not deemed persuasive to overcome the rejection of record. As stated in paragraph 5 *supra*, for the purposes of the instant rejection, the claims are interpreted to the extent that the claims read on a single active step, namely in the administration of an anti-flt-1 antibody to an undefined patient population, without any specified effective amount. Thus as acknowledged by the applicant on page 10 of the response filed 6/16/2004, Shitara *et al* does in fact teach a monoclonal antibody that is useful for the treatment of diseases associated with VEGF comprising the administration of an anti-flt-1 antibody. Furthermore, the population of patients treated, namely cancer patients, are the same and one of ordinary skill in the art would expect that the administration of the anti-flt-1 antibody would inherently treat such patients in an effective manner.

New Arguments

Claim Rejections - 35 USC § 112, 1st paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 22-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed,

had possession of the claimed invention. The written description in this case has only set forth a method of detecting leukemic cells comprising the administration of an anti-flt-1 antibody and therefore the written description in this case is not commensurate in scope to claims that read on a method of treating any disease caused by a tumorigenic change of a hematopoetic cells as claimed using any amount of an anti-flt-1 antibody as claimed.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The claims recite a treatment of a disease caused by the tumorigenic change of a hematopoietic cell as part of the invention. However, there does not appear to be an adequate written description in the specification as-filed of the broad classes of diseases that are associated with a tumorigenic change of a hematopoietic cell, nor is there support for the treatment of a disease comprising the administration of any amount of the antibody. Because the claims encompass diseases that are "caused" by such tumorigenic changes, this includes other diseases such as angiogenic diseases. For example, it is well known in the art that upon a tumorigenic change of a

hematopoietic cell, such as a white blood cells in leukemia, there is an increased incidence of angiogenesis whereby the microvessel density in the bone marrow is increased (see Perez-Atayde AR *et al* Amer. J. Pathol. 1997; 150(3):815-821 – in particular page 817). Because the claims encompass other diseases besides leukemia, and because the specification has only specifically taught the detection of flt-1 in leukemic cell lines, one of skill in the art cannot adequately determine, based on the limited disclosure of the specification, if the applicant was in possession of a method of treating the broad class of diseases, let alone leukemia. Furthermore, because there is a lack of written support for the amounts needed for effective treatment of these diseases, one of skill in the art would not be able to determine if the applicant was in possession of a treatment method because end points of "effective" treatments cannot be determined based on the limited disclosure with regard to "effective amounts" needed for such treatments.

The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see

especially page 1106 3rd column). In the instant case, the specification has not provided sufficient disclosure with regard to how the detection of the flt-1 receptor in leukemic cell lines can be correlated with the treatment of a broad class of diseases encompassed by the claims. Furthermore, the specification has not taught any definitive relationship between the detection of leukemia and how this detection can be representative or correlated to the broad genus of diseases encompassed by the claims. Applicant does not appear to have reduced to practice a representative number of diseases that can be all inclusive of the diseases instantly claimed. Neither has Applicant provided a sufficient written description of any correlation between leukemia and other diseases. Further still, the specification is devoid of disclosing any specific end points or amounts of the antibody that are required for the practice of the instant invention so as to effectively treat the broad classes of diseases claimed.

It is also noted that in claim 27, applicant claims "a protein or low molecular weight agent". The specification as filed has failed to specifically teach what these terms encompass and have not described representative species so as to be entitled to the broad class of proteins and "agent[s]"claimed and therefore the written description is not commensurate in scope to the claimed genus. The specification does not teach the conjugation of the claimed antibody to any protein or to any agent nor has the specification taught any core structure that is representative of the broad genus claimed.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43

USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001. Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 22-23,25-27,29, and 30-31 are rejected under 35 U.S.C. 102(e) as being anticipated by Rockwell *et al* (US Patent 5,840,301). For the purposes of this rejection, the claims are read to the extent that the method comprises a single active step, namely

the administration of an anti-flt-1 antibody in an effective amount to treat any disease. Rockwell *et al* teach the administration of a monoclonal anti-flt-1 antibody for the treatment of a disease comprising the administration of an effective amount of the anti-flt-1 antibody (see col. 18, claims 1-4, in particular). Rockwell *et al* further teach the administration of humanized antibodies (see col. 18, claims 7-16, in particular), antibody fragments such as Fabs or scFvs (see col. 8, lines 4-8, in particular), and that the antibody can be of the IgG subtype and more specifically IgG1 (see col. 7, lines 26-37, for example). Furthermore, because the specification does not specifically define "low molecular weight agent" as claimed in claim 27, for the purpose of this rejection any label is encompassed by this term, and therefore is anticipated by Rockwell *et al* (see col. 7, lines 8-10, in particular).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 571-272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CHY
Art Unit 1642
September 1, 2004

GARY NICKOL
PRIMARY EXAMINER